REMARKS

The present application is directed to endostatin proteins comprising a fragment of a NC1 region of a collagen protein. The proteins have the ability to inhibit angiogenesis.

Claims 52-55, 57-66, and 68-73 are pending in the above-identified patent application. Claim 52 has been amended. No new matter is introduced by the amendments. Applicants respectfully assert that the amendments to the claims do not diminish the scope of the invention as originally claimed. Based on the foregoing amendments and the following remarks, Applicants respectfully request allowance of all of the pending claims.

Rejection of Claims 52-55, 57-66, and 68-73 As Being Unpatentable Over U.S. Patent No. 5,854,205

In the office action dated October 11, 2002, the Examiner maintained the rejection of Claims 52-55, 57-66, and 68-73 under the judicially created doctrine of obviousness-type double patenting as being unpatentable over Claims 1-7 and 17-23 of U.S. Patent No. 5,854,205 for reasons of record set forth in the December 19, 2000 office action.

Applicants agree to submit a terminal disclaimer in compliance with 37 C.F.R. §3.37(b) upon allowance of the present application.

Rejection of Claims 52-55, 57-66, and 68-73 As Being Unpatentable Over U.S. Patent No. 6,346,510

In the office action dated October 11, 2002, the Examiner maintained the rejection of Claims 52-55, 57-66, and 68-73 under the judicially created doctrine of obviousness-type double patenting as being unpatentable over Claims 1-11 of U.S. Patent No. 6,346,510.

Applicants agree to submit a terminal disclaimer in compliance with 37 C.F.R. §3.37(b) upon allowance of the present application.

Rejections under 35 U.S.C. §112, first paragraph

Claims 52-55, 57-62 were rejected under 35 U.S.C. §112, first paragraph, as containing subject matter which was not described in the specification in such a way as to reasonably convey to one skilled in the relevant art that the inventors, at the time the application was filed, had possession of the claimed invention. Specifically the October 11, 2002 office action referred to reasons of record in the July 19, 2001 office action which stated that the claims are directed to an isolated protein comprising a fragment of NC1 wherein the fragment inhibits angiogenesis. According to the office action, this reads on any protein comprising NC1 or a fragment thereof.

The Examiner suggested changing "comprising" to "consisting of". In an effort to facilitate prosecution, applicants have herein amended the claims pursuant to the Examiner's recommendation. Reconsideration and withdrawal of this rejection is therefore respectfully requested.

Rejections under 35 U.S.C. §112, first paragraph

Claims 52-55, 57-62 were rejected under 35 U.S.C. §112, first paragraph, because according to the Examiner, the specification while being enabling for endostatin, does not reasonably provide enablement for a protein comprising or consisting of any fragment of NC1. The action stated that the claims encompass a protein that has a portion of the NC1 region and that although the specification makes it clear that there are specific regions needed for activity, the specification provides no guidance as to what are the required elements for activity; and accordingly, undue experimentation would be required by one skilled in the art to make and use the instant invention. Applicants respectfully traverse and submit that claimed proteins as described in relation to the term "NC1" are well defined in the specification, particularly on page 37, lines 3-15.

Proteins containing antiangiogenic fragments of a C-terminal non-collagenous region (NC1) of a collagen protein represent a novel genus described by the present specification that is defined and limited by common *structural* and *functional* features. The common *structural* feature of the members of the antiangiogenic fragment genus is that each member is a fragment of a region shared by all collagen proteins: a C-terminal non-collagenous region. Thus, the claimed proteins of the present application are structurally related because they are all fragments of structurally similar collagen proteins which are not simply any random fragments of collagen proteins, but are fragments of a region well-known to those skilled in the art. Applicants have herein amended the claim language to clarify that the present claims are directed to proteins and compositions comprising endostatin proteins, which are disclosed in the specification as having a fragment of the C-terminal non-collagenous region (page 37, lines 3-15). The present specification also teaches that the term "endostatin protein" encompasses multiple proteins within the C-terminal non-collagenous region (page 11, line 25 through page 15, line 11), wherein endostatin protein is described as including protein fragments, shortened proteins or peptides, lengthened proteins or peptides, and substituted proteins or peptides. In addition, page 14, line 25, through page 15, line 6, and page 37, lines 7-10, of the specification teach that other endostatin proteins may be isolated from other collagens. Furthermore, page 53, lines 4-7, teach the importance of the entire non-fibrillar collagen family.

A common *functional* feature shared by all members of the genus is the ability to inhibit angiogenesis. Applicants' ground-breaking discovery is that a genus of fragments of the C-terminal non-collagenous region of a collagen protein are antiangiogenic and can be used for the treatment of cancer. Page 14, lines 19-23, defines cancer as angiogenesis-dependent cancers and tumors. As mentioned above, it was known that all members of the collagen family were structurally related and had non-collagenous domains at their C-terminal ends. Examples 1-3 teach how to isolate anti-angiogenic fragments from this region. The specification further provides a method for evaluating antiangiogenic activity using assays such as the CAM assay, (page 40, lines 1-21). Therefore, Applicants respectfully submit that one of skill in the art would be able to isolate antiangiogenic fragments from any collagen, test for antiangiogenic activity, and detect the presence of endostatin proteins with an endostatin protein-specific binding antibody using the teachings of the present application.

In light of the foregoing, Applicants courteously request that the Examiner withdraw this rejection.

Rejections under 35 U.S.C. §112, first paragraph

Claims 52-55, 57-62 and 68-73 were rejected under 35 U.S.C. §112, first paragraph, because according to the Examiner, even if "comprising" is changed to "consisting of" in the claims, the claims still read an NC1 region from any collagen and thus NC1 regions from any collagen would be able to inhibit angiogenesis.

Specifically, the Examiner stated that there is no description of the conserved regions which are critical to the structure and function of the genus claimed. The Examiner stated that there is no description of the sites at which variability in the NC1 domain may be tolerated and there is no information regarding the relation of structure to function and that "structural features that could distinguish the compounds in the genus from others excluded are missing from the disclosure". According to the Examiner at the time of the applicants' invention, "the prior art did not provide compensatory structural or correlative teachings sufficient to enable one of skill to isolate and identify the inhibitory molecules encompassed and no identifying characteristic or property of the instant inhibitory molecules is provided such that one of skill would be able to predicatably identify the encompassed molecules as being identical to those instantly claimed." Applicants respectfully traverse.

As discussed above, the NC1 region is well defined in the specification, particularly on page 37, lines 3-15. Furthermore, Applicants teach in detail how to isolate fragments (Examples 1-3) and how to test for antiangiogenic activity (page 15, lines 7-25, page 40, lines 1-21).

Accordingly, based on the teachings in the specification, one skilled in the art would be able to identify antiangiogenic fragments of NC1 regions of collagen molecules. Contrary to allegations set forth in the office action, Applicants claim isolated proteins consisting of fragments of NC1 regions of collagen molecules and clearly define how to identify such fragments by providing detailed teachings of isolating and testing antiangiogenic fragments.

The Examiner further states that while each collagen does have a NC$_1$ domain, the specification only shows that NC domains containing SEQ ID NOS. 1 or 2 have antiangiogenic activity. According to the Examiner, a sequence search for SEQ ID NOS. 1 and 2 revealed very little homology among the group of 18 collagen molecules that are known. Applicants respectfully submit that they have identified a novel genus of antiangiogenic molecules comprising NC domains of collagens and active fragments thereof. The antiangiogenic proteins comprising SEQ ID NOS. 1 and 2 are merely representative members of this genus. Applicants discovery encompasses antiangiogenic fragments of NC1 domains of collagen molecules, and this discovery is not limited to fragments comprising only SEQ ID NOS: 1 or 2. Since it is not necessary to provide each and every species where the genus is well defined, applicants respectfully maintain that the subject matter of the claims is well described.

Furthermore, the lack of homology among the collagen molecules as discussed by the Examiner, actually supports the novelty and patentability of Applicants' invention. Given the disparity in the sequences one would not expect NC domains of such molecules to have similar activity, more particularly it would not be obvious based on sequence identification that the molecules would have comparable effects on angiogenesis. Applicants' novel discovery provides that specific domains of molecules having disparate sequence identities have similar functions.

Based on the foregoing, Applicants respectfully submit that the subject matter of Claims 52-55, 57-62 and 68-73 is sufficiently described such that one skilled in the art would readily appreciate that the inventors, at the time the application was filed, had possession of the claimed invention. Reconsideration and withdrawal of this rejection is therefore respectfully requested.

Rejections under 35 U.S.C. § 102

In the office action dated July 19, 2001, the Examiner rejected Claims 52-54 and 57-62 under 35 U.S.C. 102(e) as being anticipated by Olsen *et al.*, (US Patent No. 5,643,783, 1993). Applicants respectfully traverse. Reconsideration and withdrawal of this rejection is therefore respectfully requested.

Olsen *et al.* merely teach a method of expressing the entire collagen type XVIII protein. The present claims recite inhibitory proteins which are identified as fragments of the NC1 region of collagen molecules that possess antiangiogenic activity. Olsen *et al.* do not teach or suggest methods directed to expressing inhibitory protein fragments which form a heretofore undiscovered genus of antiangiogenic NC1 fragments of collagen proteins. Therefore, Olsen *et al.* fail to anticipate the claims.

In light of the above, Applicants respectfully submit that Claims 52-55, 57-66 and 68-73 are allowable, and a Notice of Allowance is courteously solicited. The foregoing is submitted as a full and complete response to the Office Action mailed October 11, 2002 in United States Patent Application Serial No. 09/405,499. The Examiner is invited and encouraged to contact the undersigned attorney of record if such contact will facilitate an efficient examination and allowance of the application.

Respectfully submitted,

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Amendments To The Claims
(Marked Up Version)

Please amend the following claims by deleting the words in brackets and inserting the underlined words.

52. (Twice Amended) An [isolated] endostatin protein [comprising] consisting of a fragment of a NC1 region of a collagen protein, wherein the fragment inhibits angiogenesis.